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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/803,566	03/18/2004	Andrew James Ratcliffe	USCA2206 US CNT	5977

5487 7590 01/24/2005

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EXAMINER	
TUCKER, ZACHARY C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/803,566	RATCLIFFE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1Dec04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants may opine that one of ordinary skill understands what the term "prodrug" means. The examiner is not pretending that one of ordinary skill does not understand what *function* a prodrug serves. This is not the issue here. What is claimed is chemical compounds which serve as a prodrug for the compounds of formula (I). The claim, therefore, is drawn to a group of *molecular structures*, that when subjected to a biological milieu in a live animal, will be metabolically converted to a compound of formula (I). One of ordinary skill cannot possibly be aware of the full scope of all of the different molecular arrangements which will provide the compounds (I) upon being metabolized, in all animals. Page 14 of the specification only provides a few examples of what applicants intend the term to encompass. The only type of prodrug discussed is ester derivatives.

As evidenced by the Al-Dabbagh and Smith reference, cited *infra*, in the rejection of the claimed prodrugs under the first paragraph of 35 U.S.C. 112, animals will differ significantly in the manner that xenobiotics are metabolized. Therefore, a compound that is a prodrug in humans is not necessarily a prodrug in a cat, for example.

Amendment to replace all recitations throughout the claims of "prodrug" with "prodrug esters" would overcome the indefiniteness rejection based on "prodrug."

Since all claims depend from claim 1, which is indefinite, all claims are indefinite. However, the "prodrugs" limitation is repeated in claims 2-8 as well, rendering those claims further indefinite for that reason.

Claim 10 is further indefinite, in addition to depending from an indefinite claim, because it is unknown what the full scope of "diseases capable of being modulated by inhibition of JNK activity" is. As will be seen in the rejection of claim 10 under the first paragraph of 35 U.S.C. 112, *infra*, this phraseology embraces those diseases made worse by (that is up-modulated) JNK activity inhibition.

What is problematic with the language of claim 10 is that one of ordinary skill is not aware of the full scope of those diseases capable of being modulated by inhibition of JNK activity. The claim's language actually implies that the full scope is in fact unknown, because "capable" does not require that 1. The compound of the invention is the entity that inhibits JNK activity (it could be some other agent that inhibits the enzyme) and 2. that the diseases embraced by the claim language were recognized as having this property at the time the invention was made, because they might have the required capability, but this property is unknown.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the synthesis of compounds of formula (I) and the corresponding N-oxides and pharmaceutically acceptable salts thereof, does not reasonably provide enablement for the full scope of all prodrugs of a compound of formula (I), and N-oxides of the prodrugs, all solvates of a compound of formula (I) and the N-oxides of the solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Wands factors provide a guide for determining the scope of enablement provided by a given disclosure:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) Though it might appear that the scope of instant claim 1 is limited to compounds of formula (I) having the structure depicted, it is not. A prodrug, as defined by Bundgaard in:

Hans Bundgaard, Design of Prodrugs, page 1. © 1985 Elsevier Science Publishers.

"is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug." Thus, an important requirement of prodrugs of compounds having the formula (I) is that they be pharmacologically inactive. Prodrugs come in myriad forms, and are not limited to only carboxylic esters, which are most commonly cited as examples, and suggested as the preferred type of prodrug on page 14 of the instant specification. A prodrug may be an amide, a Mannich base (imine), an acyclic precursor to a cyclic compound, a polymer-bound drug (either covalently or ionically), a compound of the drug covalently or ionically bound to another drug with different action or a carboxylic acid which is decarboxylated to provide the active drug.

So, the scope of all prodrugs is quite broad. A prodrug does not depend on the identity of the pharmacologically active agent formed from the prodrug for patentability. A prodrug is not necessarily even structurally related to the compound of which it is a prodrug, since the metabolism *in vivo* of that compound is what provides the drug.

(B) Prodrugs of a compound having the formula (I) are the nature of the invention. These are chemical compounds.

(C) The state of the prior art with respect to the development of prodrugs is represented by:

Richard B. Silverman, The Organic Chemistry of Drug Design and Drug Action, pages 352-400. © 1992 Academic Press, Inc.

Silverman teaches many kinds of prodrugs, including all of the types mentioned above in section "(A)." Pages 353 and 354 list eight various reasons why a prodrug would be desirable. On page 354, Silverman teaches that some prodrugs are

discovered accidentally, and some designed on the basis of known metabolic transformations.

(D) The level of ordinary skill in the art is that of a medicinal chemist, holding a graduate level degree in the field and with experience in preparative organic chemistry.

(E) As discovery of prodrugs is sometimes accidental, then it follows that whether a given compound will function as a prodrug or not is sometimes unpredictable. On the other hand, when a compound is designed as a prodrug, one must first understand the metabolic milieu into which the presumptive prodrug is to be introduced, and must also know to what extent the compound will be metabolized. The metabolism of xenobiotics is not always predictable. A prodrug must also, by definition, be pharmacologically inactive, so one must know which modifications of the structure of the parent compound will render it inactive. Structure-activity relationships must in large part be determined empirically, although once a rule is discerned, the structure-activity of a given series of compounds becomes predictable.

Theoretically, if one of ordinary skill in the art knew all of the above variables, prodrug structure could be predicted in advance. The reality is that all of these considerations, in total, must be empirically devised when the compound in question is a novel compound, as is the compound having formula (I).

(F) Applicants rely on some literature citations as direction for the preparation of prodrugs of compounds having the formula (I). No metabolic studies of the compounds *in vivo* have been done and no structure-activity rules are outlined – certainly no teaching as to which modifications will afford an *inactive* compound is found in the

specification. The specification does not specifically address any type of prodrug other than carboxylate esters at page 14.

(G) No working examples, out of the hundreds of preparative examples, of a prodrug are in the disclosure.

(H) In order for one of ordinary skill in the art to practice the full scope of the prodrugs of compounds having the formula (I), a complete structure activity analysis would have to be completed. The practitioner would first screen for which type of modifications of the molecular structure would render an inactive compound. Then, the metabolic studies of all of the inactive compounds would have to be completed, and compounds that are converted to active compounds of formula (I) *in vivo* identified. This research would potentially be inconclusive and could take years. Additionally, one of ordinary skill in the art would necessarily have to undertake an effort to make totally new compounds not bearing any structural similarity to the compounds having the formula (I), such as the procyclic compounds converted to heterocyclic compounds *in vivo*, which are mentioned on page 360 of Silverman. Work with polymeric forms of the compounds having formula (I) would be necessary also. Because different animals' metabolisms differ to the extent that xenobiotics are handled by different enzymatic pathways, this effort would have to be duplicated in each species for which a prodrug were sought. As evidence that animals will differ substantially in the manner that xenobiotics are metabolized, the examiner presents:

> Al-Dabbagh and Smith, "Species differences in oxidative drug metabolism: some basic considerations." Archives of toxicology. Supplement. Archiv fur Toxikologie. supplement, vol. 7, pages 219-231 (1984).

Al-Dabbagh and Smith states that the metabolic process itself is highly variable both between and within animal species, and that the toxic effect of many chemicals is a function of how the chemical is metabolized rather than the substance itself.

Given the amount of direction in the disclosure, this amount of experimentation is clearly undue. Applicants have not described manner and process of making prodrugs of compounds having the formula (I), in such full, clear, concise, and exact terms as to enable any person skilled in the art to do so.

(A) Insofar as the solvate embodiment of claims 1-10 is concerned, those claims read on solvates of compounds according to formula (I), a pharmaceutical composition (claim 9) comprising solvates of compounds according to formula (I), and methods according to claim 10 wherein a solvate of a compound according to formula (I) is employed as the therapeutic agent. The scope of the solvates recited in the claims includes solvates of a compound according to formula (I), with *any* solvent. The definition of a solvate, taken from the Vippagunta et al reference, cited in section (C), (D), (E) below, is a "crystalline solid adduct[s] containing solvent molecules within the crystal structure, in either stoichiometric or nonstoichiometric proportions, giving rise to unique differences in the physical and pharmaceutical properties of the drug."

(B) The nature of the invention is that of a chemical compound, a pharmaceutical composition or a medical treatment method.

(C), (D), (E) Solvates, at the time the invention was made, were known, but not to such an extent that the preparation of those solvates other than hydrates was routine or

simple. The following references address the state of the art with respect to crystalline forms of organic compounds, formation of solvates of organic compounds, and the predictability thereof.

Vippagunta et al, "Crystalline Solids" Advanced Drug Delivery Reviews, vol. 48, pages 3-26 (2001).

and

Gavezzotti, "Are Crystal Structures Predictable?" Accounts of Chemical Research, vol. 27, pages 309-314 (1994).

First, it is evident from both of the references that formation of specific crystalline forms, and more particularly, solvates, is highly unpredictable. See Gavezzotti, page 312, point #8, and Vippagunta et al, page 11, "Prediction of Polymorphs" and page 18 "Prediction of the formation of hydrates and solvates."

Because the formation of solvates is unpredictable, even the relatively high level of skill possessed by one of ordinary skill in the art is not enough to render preparation of solvates routine. Each solvate of each compound must be experimentally prepared (since the conditions necessary for the formation cannot be predicted), wherein all of the factors relevant to each individual compound's ability to crystallize and form solvates are studied. These factors are identified in points #1-7 of the Gavezzotti reference. The preparation of each single claimed solvate represents a significant undertaking in the areas of preparative organic chemistry, physical chemistry, and crystallographic measurements.

It is unknown that the full scope of solvates of compounds of formula (I) is even possible (see Gavezzotti, page 309, point #1).

(F) Aside from a mention that the invention includes solvates, preferably hydrates, no guidance relevant to preparation of solvates is provided in the disclosure.

(G) No working examples, out of the hundreds provided, demonstrate preparation of a solvate. In fact, compounds of the invention are crystallized from a variety of solvents throughout the working examples, yet not solvate is identified.

(H) Each compound of formula (I), of which there are thousands, as a solvate with every solvent within the scope of "solvate" generally, of which there are also thousands, represents the efforts of many over a period of years. Those efforts are potentially inconclusive. For one of ordinary skill in the art to conduct the type of research outlined in Gavezzotti and in Vippagunta et al for preparation of every one of the claimed solvates would be undue. Applicants' right to exclude others from making all solvates of compounds according to formula (I) is unwarranted in light of the lack of any direction as to how one of ordinary skill would do so.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Diseases made worse by inhibition of JNK activity are included in the broadest reasonable interpretation of the phrase "capable of being modulated by inhibition of JNK activity." These diseases cannot possibly be treated by administering a compound of the invention. A *prima facie* case of lack of enablement exists in this reqard.

As evidence that there are some diseases made worse by JNK inhibition, the examiner submits:

Kennedy et al, "Suppresion of Ras-stimulated transformation by the JNK signal transduction pathway" GENES & DEVELOPMENT, vol. 17, pages 629-637 (2003).

At page 630, the statement –

"JNK deficiency causes profound increases in the number and growth of Ras-induced tumor nodules in vivo. Thus, the JNK signaling pathway functions to suppress the oncogenic effects of Ras."

appears in column 1 (top).

It is evident that a compound of the invention would exacerbate Ras-mediated cancers (which includes many common cancers), therefore claim 10 is not enabled.

Title, Abstract and Specification

The title of the instant application "Chemical Compounds" does not adequately the invention. Almost any proposed title which is more descriptive of the invention than the present title would be acceptable. See 37 C.F.R. 1.72(a). The examiner suggests "JNK Inhibitors" as a revised title of the application.

The abstract of the disclosure is objected to because it is too long. An abstract for publication cannot exceed 150 words (37 C.F.R. 1.72(b)) Correction is required. See MPEP § 608.01(b).

No brief description of the drawings section appears in the body of the disclosure, therefore the specification is objected to under 37 C.F.R. 1.74. When there are drawings, a section headed "Brief Description of the Drawings" must appear in the specification.

Correction of the above-noted deficiencies in this section are necessary before the application is allowed to pass to issue, as these objections are based on direct violation of patent rules.

Allowable Subject Matter

Compounds of formula (I) are allowable over the prior art. The closest prior art comes from WO 01/072752 (Ennis et al). The Ennis et al publication teaches 5-HT antagonists having a molecular structure similar to the compounds according to the instant invention, however, Ennis et al's compounds differ in that the nucleus is tricyclic, not bicyclic as required by the instant claims. In instant claim 1, R^2 and R^3 cannot be joined to form a ring, differentiating from Ennis et al.

Deletion of "prodrugs" in all occurrences and replacing with "prodrug esters" would overcome the rejections under 35 U.S.C. 112 of claims 1-10 on grounds of nonenablement and indefiniteness of "prodrug" generally.

Replacing "solvates" with "hydrates" would overcome the rejection under 35 U.S.C. 112, first paragraph on grounds that the full scope of all solvates is not enabled by the disclosure.

Claim 10, should be rewritten as follows, or deleted and replaced with a claim 11 that reads as follows, would be allowable.

(claim no.) A method of inhibiting JNK activity in a patient, comprising administering an effective dose of a compound according to claim 1 to the patient.

Applicant is advised that the "in need thereof" limitation should NOT be included in a claim as suggested by the examiner in the preceding paragraph (it does not appear in the proposed claim). This clause would render the claim indefinite in scope.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 6:15am to 2:45pm, Monday from 6:15am to 1:45pm and Friday from 6:15am to 3:45pm (EST). If Attempts to reach the examiner are unsuccessful, the examiner's supervisor, Mukund Shah, can be reached at (571) 272-0674.

If, after a 24-hour period, Dr. Shah is unreachable, contact the examiner's acting supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

zt

JAMES O. WILSON
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